

Cucurbitacins are Natural Anticancer Compounds Found in Plants of the Cucurbitaceae Family

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Abstract

Background: Cucurbitacins are important compounds in the Cucurbitaceae family. They are known for their potential in cancer treatment. Cucurbitacins have a complex structure with over 200 variants, each exhibiting different biological activities. Ongoing research aims to enhance their effectiveness in medicine.

Objectives: The study aimed to identify compounds with the potential to be used in chemotherapy by examining the structure of Cucurbitacins found in plants of the Cucurbitaceae family.

Methods: In this review study, we analyzed the biological and anticancer activities of plant compounds known as Cucurbitacins. We searched for keywords such as "Cucurbitacins", "Cucurbitaceae family", "Antioxidants", and "Anticancer" in databases including Google Scholar, PubMed, and Scopus. We gathered information about Cucurbitacins from PubChem, searched for Cucurbitacin, and refined results using advanced options.

Results: The anticancer potential of Cucurbitacins has been extensively researched. Specific Cucurbitacins, such as D, E, I, and IIa, have been found to induce cell death and autophagy in cancer cells, inhibit their migration and invasion, arrest the cell cycle, and impede their proliferation and survival. These compounds also inhibit the JAK2/STAT3 pathway, which is implicated in various cancers, including breast, pancreatic, colon, ovarian, and osteosarcoma. Recent interest in Cucurbitacins has surged for their potential in cancer prevention and treatment. Some studies suggest that consuming fruits and vegetables rich in Cucurbitacins may reduce the risk of certain cancers. Furthermore, they hold promise as chemotherapeutic agents in combination with conventional treatments.

Conclusion: The ability of Cucurbitacins to inhibit cell proliferation, induce apoptosis and autophagy, inhibit cell migration and invasion, and block the JAK/STAT3 signaling pathway make them potential candidates for cancer prevention and treatment.

Keywords: Cucurbitacin, Antioxidants, Anticancer

1. Background

Cucurbitacins are primarily found in the Cucurbitaceae family, which consists of 120 genera and 965 plant species. They are commonly found in various vegetables and fruits. Cucurbitacins can also be found in other plant families such as Begoniaceae, Cruciferae, Datisceae, Desfontainiaceae, Euphorbiaceae, Elaeocarpaceae, Scrophulariaceae, Polemoniaceae, Primulaceae, Rubiaceae, and Sterculiaceae. However, they are predominantly found in the Cucurbitaceae family and in genera such as *Bryonia*, *Cucumis*, *Cucurbita*, *Luffa*, *Echinocystis*, *Lagenaria*, *Citrullus*, *Sechium*, and *Momordica*. Examples of plants that contain cucurbitacins include cucumbers (*Cucumis sativus*), pumpkins (*Cucurbita moschata*), watermelons (*Citrullus lanatus*), melons (*Cucumis melo*), gourds (*Cucurbita pepo*), bottle gourds (*Lagenaria siceraria*), a type of melon (*Luffa acutangula*), and *Bryonia dioica*. A specific type of cucurbitacins called momordicosides can be found in *Momordica charantia* (bitter melon or African

cucumber). Cucurbitacins can also be found in certain fungi and a shell-less marine mollusk.¹⁻⁵

Cucurbitacins such as CuB or CuE are primarily stored in the roots of plants, while CuD, CuB, CuI, and CuE are more commonly found in the cotyledons of plants. CuB and CuE are usually present in larger quantities. These types of cucurbitacins are believed to be the first bitter compounds formed during growth. Plants with local bitter taste genotypes tend to have high concentrations of CuB and CuD in the absence of CuI and CuE. Cucurbitacin B, isolated from *Trichosanthes cucumerina*, is known for its anticancer properties. *Cucumis sativus* (cucumber) is a well-known plant that is rich in cucurbitacins A, B, C, D, and E. Our narrative review indicates that Cucurbitacins have anticancer properties through several mechanisms. They can induce programmed cell death and autophagy in cancer cells, stop the cancer cell cycle, hinder cell migration and invasion, and interfere with growth signals. Cucurbitacins may also enhance

chemotherapy effects and exhibit anti-inflammatory and antioxidant properties. However, issues such as low bioavailability and toxicity remain. More research is needed to explore their potential in cancer prevention and treatment.^{3,4}

2. Objectives

In this study, we aimed to identify compounds with the potential to use in chemotherapy by examining the structure of Cucurbitacins found in plants of the Cucurbitaceae family.

3. Methods

3.1. Review of Scientific Literature

Our review was based on studies that investigated the effects of various types of cucurbitacins extracted from

plant compounds on cancer cell cultures. This study utilized a narrative review approach to explore the anticancer properties of cucurbitacins. We carefully analyzed articles from reputable databases such as Google Scholar, Scopus, and PubMed. The research focused on keywords such as "Cucurbitacins", "Cucurbitaceae", "Antioxidants", and "Anticancer" to investigate the potential health benefits and properties of these subjects within the Cucurbitaceae plant family. We gathered information about Cucurbitacins from PubChem, searching for Cucurbitacin and refining results using advanced options.

4. Cucurbitacins

Cucurbitacins are triterpene saponins of the cucurbitane type, consisting of four rings and containing 30 carbon atoms.

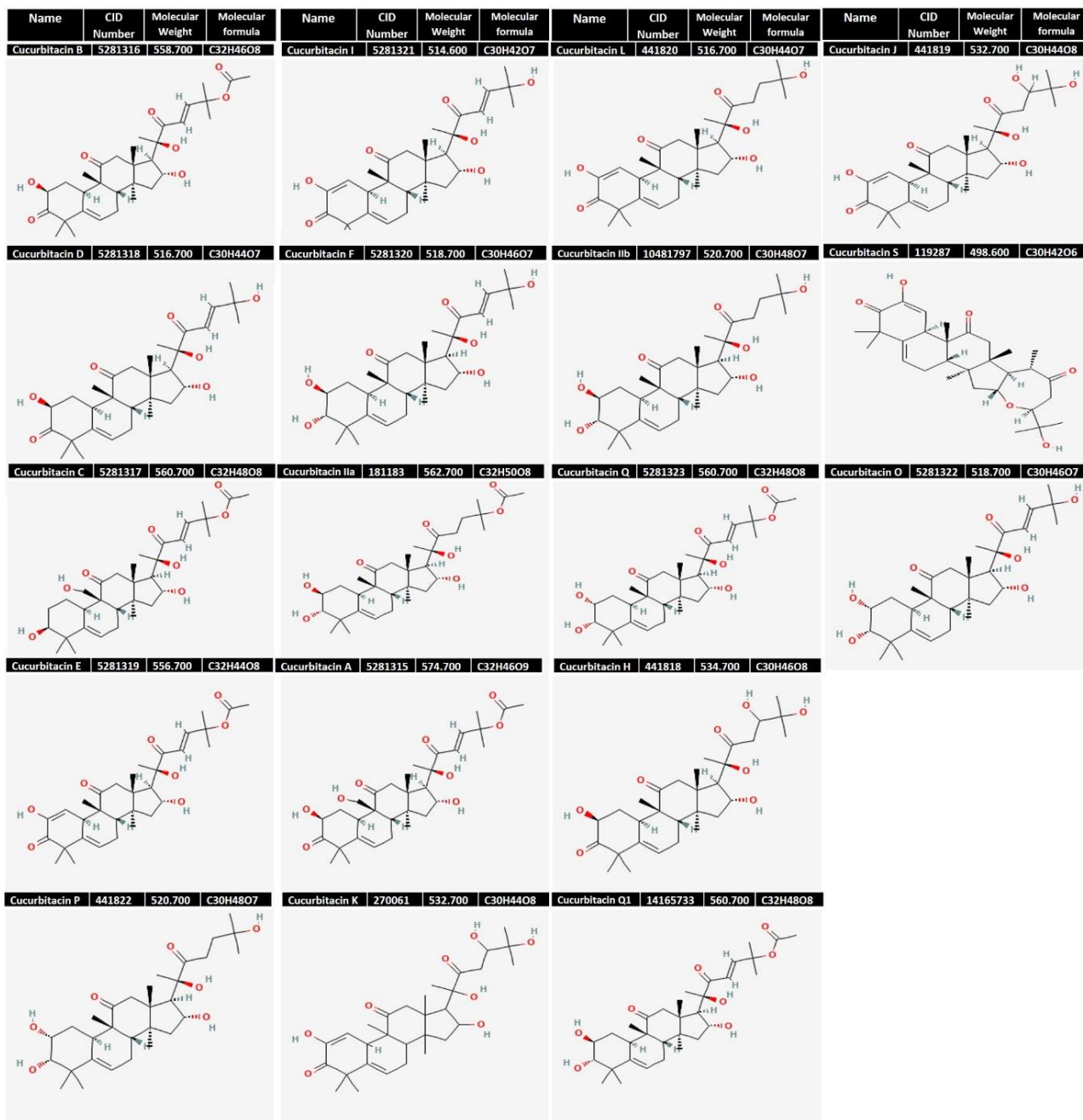


Figure 1. Types of Cucurbitacin Found in Herbal Compounds (6).

They are produced by plants in the Cucurbitaceae family and can be divided into 12 groups, labeled A to T. The focus of research is primarily on four specific cucurbitacins: B (CuB), D (CuD), E (CuE), and I (CuI). These cucurbitacins exhibit variations in the arrangement of acetyl groups on carbon C25 and hydroxyl groups on carbon C2. At the core of their molecular structure is the cucurbitane core (19-(10 \rightarrow β)-abeo-10 α -lanost-5-ene), which is located in the center of the molecule. Some of the main cucurbitacins found in natural products include CuB, CuE, CuD, CuI, CuIIa, and CuIIb. The primary differences in their structure lie in the substitution pattern on ring A (C1-C5) and on the side chain, where unsaturated groups may be present at C23 and C25, as well as an acetyl group at C25. Additionally, there may be alpha and beta hydroxyl groups at C2, C3, C7, C9, C16, and C20 to C25. Unsaturated carbons at C23 to C25 and keto groups at C2, C3, C11, C15, and C22 may also form⁵⁻¹⁰ (Figure 1).

5. Therapeutic Effects of Cucurbitacin

Cucurbitacins have a wide range of therapeutic effects, including antioxidant, anti-inflammatory, blood sugar-lowering, liver-protecting, heart-protecting, anticancer, antimicrobial, antihelminthic, and antiviral properties. The anticancer effects of cucurbitacins are attributed to their ability to induce autophagy, apoptosis, and control cell proliferation. Certain derivatives of cucurbitacin have also been found to have significant biological effects.¹⁰⁻¹⁵ Notably, cucurbitacin B and E play a role in both innate and acquired immunity. By inhibiting cyclooxygenase-2 and nitric oxide synthetase, cucurbitacins help reduce oxidative stress, suppress proinflammatory cytokines, and regulate immune proteins in the acquired immune system. Cucurbitacin E specifically inhibits the enzymes COX and RNS, which are associated with severe inflammatory responses in various chronic inflammatory conditions. Cucurbitacin B and E have also shown anti-aging effects on cells, with cucurbitacin B increasing the proliferative capacity and long-term survival of cells in the mutant yeast strain *Saccharomyces cerevisiae* K6001 by modulating autophagy and antioxidant activity, thereby prolonging their lifespan. Additionally, cucurbitacin B enhances the bioavailability of warfarin and enhances its anticoagulant potential. Cucurbitacin B, D, and E have the ability to increase the interaction between albumin and drugs. Furthermore, studies have shown that cucurbitacin B, D, and E exhibit antiviral potential against Hepatitis C Virus (HCV) and Bovine Viral Diarrhea Virus (BVDV). In the case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), cucurbitacin analogs like cucurbitacin-G2 glucoside have been found to effectively bind to and inhibit the major protease protein (Mpro) of the coronavirus. It is possible that the inhibitory mechanism of cucurbitacin-G2-

glucoside on the Mpro-SARS-CoV-2 protease also inhibits the activity of helicase enzymes involved in the virus replication cycle. Moreover, cucurbitacins have been shown to have inhibitory effects on cancers by targeting signaling pathways related to STAT3, JAK-STAT, ERK, and MAPK factors.^{16,17}

6. Anticancer Effects of Cucurbitacin

CuB, CuD, CuE, CuI, and CuIIa have various effects on apoptosis, autophagy, cell migration and invasion, cell cycle arrest, inhibition of cell growth and survival, and anti-inflammatory processes. Cucurbitacins often exhibit anticancer effects by inhibiting the JAK/STAT3 pathway, which is involved in cancer development. Janus Kinase (JAK) is a family of tyrosine kinases that includes JAK1, JAK2, JAK3, and TYK2. These transcription factors are activated when cytokines bind to their receptors, leading to phosphorylation and activation of the Signal Transducer and its Activators Transcription (STAT) factor.^{18-20,27}

Cucurbitacins regulate the expression of genes related to proliferation mechanisms, such as cyclins and c-myc, while repressing the expression of anti-apoptotic genes like Bcl-XI and Bcl-2. The JAK kinase family is activated in many hematopoietic malignancies and several cancers, including bladder, colon, cervical, medulloblastoma, leukemias, and lymphomas. CuB inhibits the Epidermal Growth Factor Receptor (EGFR) and hinders the growth of pancreatic cancer cells by enhancing the presence of pro-apoptotic protein Bim and increasing apoptosis frequency through negative regulation of anti-apoptotic proteins like Bcl-2. Cucurbitacins prevent STAT3 from binding to DNA, reducing the levels of phosphorylated JAK, STAT3, and downstream target proteins like Bcl-2 in cancer cells, ultimately promoting apoptosis. CuE significantly affects apoptosis in bladder cancer cells by reducing STAT3 phosphorylation and activating mitochondria-dependent signaling pathways through caspase-8 and caspase-3. Cucurbitacins also contribute to cell cycle arrest in cancer cells by inhibiting genes that encode cyclins. CuB induces cell cycle arrest at the G2/M phase and initiates apoptosis in cancer cells by inhibiting JAK2, STAT3, and STAT5, as well as reducing Bcl-XI. In human hepatocellular carcinoma cells, CuB downregulates the expression of cyclins D1 and cdc-2, which are involved in the progression of the G2/M phase.¹⁸⁻²¹

CuB has anticancer activity due to its inhibitory effect on the JAK/STAT pathway and metabolic pathways that promote tumor cell growth, such as NF κ B, PI3K/Akt/mTOR, and MAPK/ERK. The Wnt/ β -catenin pathway induces the expression of tumor suppressor genes, such as p53, promotes apoptosis, regulates cell survival, and inhibits the overexpression of oncogenic factors. Cucurbitacins also inhibit the Raf/MEK/ERK pathway, which is involved in the regulation of cell proliferation, growth, differentiation,

and senescence in leukemic cells. CuB can affect the Raf/MEK/ERK and JAK/STAT3 signaling pathways in leukemic cells, inhibiting their growth. CuE inhibits mTORC1 signaling by reducing mTORC1 activity, which is an essential pathway for regulating the autophagy process. It also activates the transcription factor ULK1, an autophagy promoter, and induces autophagy in human cancer cells.²²⁻²⁴

CuI reduces invasion of colon cancer cell lines by decreasing STAT3 phosphorylation and MMP-9 expression. CuB induces apoptosis and inhibits the proliferation of lung cancer cell lines by disrupting the specific inactive transcript of lncRNA X (XIST), which has also been reported in colon and breast cancer tumors. CuB induces apoptosis through positive regulation of miR-let-7c. Additionally, CuB inhibits proliferation and invasion of human Glioblastoma Multiforme (GBM) cell lines and reduces the expression of the oncoprotein CIP2A and its downstream signaling molecules. CuB acts as a CIP2A inhibitor.^{25,26}

CuB, administered at doses of 12.5 mg, 25 mg, and 50 mg/kg body weight for 12 days, significantly reduces alveolar bone loss in periodontitis by regulating RANK/OPG levels and reducing inflammatory responses. In U-2 OS osteosarcoma cells treated with CuB, there is a notable decrease in the levels of transcription factors p38, ERK1/2, JNK, and p-JNK. This decrease in the expression of transcription factors of the MAPK pathway is an important mechanism in inducing apoptosis in U-2 OS cells.²⁷

Apoptosis is induced in Non-Small Cell Lung Cancer (NSCLC) cells by inhibiting matrix Metalloproteinases (MMPs) and interleukin-6 (IL-6) through the TLR4/NLRP3/GSDMD pathway. CuB inhibits angiogenesis by suppressing the mitochondrial signaling pathway, inhibiting Vascular Endothelial Growth Factor (VEGF), and subsequently deactivating Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) in endothelial cells. Furthermore, CuB hinders metastasis by deactivating epithelial-mesenchymal transition under TGF- β 1 stimulation in NSCLC cancer cells. This is achieved through the regulation of Reactive Oxygen Species (ROS) and the PI3K/Akt/mTOR signaling pathways.²⁸⁻³⁰

6.1. Cucurbitacin in Breast Cancer

Breast cancer is the second leading cause of death in women. Treatment of MCF-7 breast cancer cells with cucurbitacin B alone or in combination with imatinib mesylate inhibits cell proliferation and induces apoptosis. There is a synergistic effect of gemcitabine or docetaxel with cucurbitacin B, which increases apoptosis and prevents proliferation of MDA-MB-231 breast cancer cells under laboratory conditions. This treatment also decreases tumor volume without increasing toxicity. Additionally, cucurbitacin B, when combined with ionizing

radiation, blocks cancer cells in the G2/M phase, promotes apoptosis, and inhibits cancer cells. It decreases the transcription factors p-STAT3, c-Myc, Bcl-2, and Bcl-xL, while increasing levels of molecules related to apoptosis, such as caspase-9, p21, and p53. In another study, the glycosylated form of CuB and CuE halts the passage of breast cancer cells through the G2/M phase and causes changes in cell morphology associated with actin filament changes. Alterations in the cytoskeleton, specifically actin chains, are another mechanism of cucurbitacins leading to cell death in different types of cancer cell lines. This is due to the direct alteration of the actin chain polymerization process. Cell cycle arrest in the G2/M phase and induction of apoptosis in many cancer cell lines may be caused by the disruption of STAT3 phosphorylation or a decrease in the expression of Bcl-2 and cyclin B1. Alterations in cytoskeletal composition have also been observed in myeloid leukemia.³¹⁻³³

In breast cancer, CuB prevents adhesion and viscoelasticity of various cell lines. It also inhibits invasion and migration of malignant cells by suppressing the expression of F-actin and vimentin. The proteins FAK and vinculin regulate the distribution and organization of the cytoskeleton. CuB hinders the RAC1, CDC42, and RhoA signaling pathways, which are associated with cell survival and migration, thereby impeding cancer cell metastasis. Aberrant methylation serves as a stimulus in tumor development, and the role of methylation in cancer cell growth is linked to the abnormal expression of genes related to growth factors. CuB, found in *Trichosanthes cucumerina*, acts as an anti-hypermethylating agent that reduces the expression of the oncogenic drivers c-Myc and cyclin D1. Accordingly, nowadays it is being considered for use in the treatment of breast cancer.³⁴

6.2. Cucurbitacin in Pancreatic Cancer

Pancreatic cancer boasts the highest mortality rate among cancers, with a 95% mortality rate after five years. It is also known for being insensitive to chemotherapy and radiotherapy. However, there is a glimmer of hope in the form of cucurbitacin B, in combination with an ERK inhibitor called SCH772984. This duo has shown promising results in inhibiting the growth and proliferation of pancreatic cancer cells. It achieves this by targeting the growth factor receptor EGFR and its downstream signalling pathways, which include PI3K, Akt, mTOR, and STAT3. Through this targeting, apoptosis, or programmed cell death, is induced. Additionally, the combination leads to an increase in pro-apoptotic proteins like Bim, while reducing anti-apoptotic proteins such as McL-1, Bcl-2, Bcl-xL, and survivin. Consequently, there is a noticeable decrease in both the volume and weight of the tumor.³⁵

6.3. Cucurbitacin in Colon Cancer

Colon cancer is the fourth leading cause of cancer-related

death worldwide in both men and women. Bacterial and fungal infections associated with this disease can worsen the prognosis. Increased expression of the epithelial growth factor receptor EGFR and transcription factors that activate its downstream signaling pathways, such as JAK/STAT, indicate this type of cancer. When SW480 colorectal cancer cells are exposed to cucurbitacin B alone or in combination with imatinib mesylate, it synergistically inhibits cancer cell proliferation and induces apoptosis. Additionally, cucurbitacin B may enhance the inhibitory effect of imatinib mesylate on the expression of the enzyme matrix metalloproteinase-2 (MMP-2). The MMP family destroys the extracellular matrix, enabling cancer cell migration and invasion.³⁶

6.4. Cucurbitacin in Ovarian Cancer

Platinum-based drugs, such as cisplatin, are commonly used in the treatment of ovarian cancer. However, in many cases, the tumor can recur and develop resistance to cisplatin. Cucurbitacin B has shown cytotoxic effects on the ovarian cancer cell line A2780. When the cisplatin-resistant cell line A2780 is pre-treated with this natural compound, the cytotoxicity of cisplatin increases.

Furthermore, Cucurbitacin B has also demonstrated dose- and time-dependent cytotoxicity on taxol-resistant human ovarian cancer A2780 cells. These cells are arrested in the G2/M phase of the cell cycle through various molecular mechanisms, including upregulation of p53 and p21, reduction of Bcl-2, activation of caspase-3, and suppression of P-gp.³⁷

6.5. Cucurbitacin in Osteosarcoma

Osteosarcoma is the most prevalent malignant bone tumor in children and adolescents, with the highest incidence seen in individuals between the ages of 15 and 19. Treatment usually consists of surgery, radiation, and chemotherapy. A low-dose combination of cucurbitacin B and methotrexate has been shown to synergistically inhibit AKT and mTOR signaling pathways in human osteosarcoma cells, both in vivo and in vitro, resulting in enhanced tumor suppression rates.^{22-24, 27}

7. Toxicity and Side Effects of Cucurbitacins

Cucurbitacins, particularly cucurbitacin E (Cu E), are known for their toxic and potential therapeutic effects. These compounds can be poisonous, especially when present in the bitter fruits of plants from the Cucumis and Cucurbita genera. Historical records document cases of severe poisoning in livestock, and the bitterness of these fruits typically deters humans from consuming them in harmful quantities. Nevertheless, instances of human poisoning have occurred, underscoring the importance of accurately identifying edible plants within the Cucurbitaceae family.^{38,39}

Research is currently exploring the therapeutic properties

of CuB, a copper-based compound, for cancer treatment. CuB exhibits moderate toxicity towards both cancerous and normal cells, with lower doses preferentially affecting cancer cells. Studies suggest that CuB does not cause significant harm to major organs in animal models. Preclinical research has demonstrated that CuB can effectively eliminate NSCLC cells while sparing normal lung cells at low concentrations. However, further investigations are needed to assess the effects of CuB on human colorectal carcinoma cells, establish its safety profile, and elucidate the mechanisms underlying its selective toxicity.⁴⁰⁻⁴³

8. Discussion

The ongoing effort to discover compounds with anticancer properties of plant origin has always been valuable. In this study, we aimed to identify compounds with the potential to use in chemotherapy by examining the structure of Cucurbitacins found in plants of the Cucurbitaceae family. The roots and fruits of plants belonging to the Cucurbitaceae species are known to be very bitter, but they possess a wide range of medicinal activities, including anti-inflammatory and anticancer effects.^{18,19} They have been found to inhibit the proliferation of cancer cells and induce apoptosis. Cucurbitacin, a compound found in these plants, plays a key role in regulating actin fiber, STAT, and cyclooxygenase-2 to inhibit cancer cells. The structures of cucurbitacins consist of a four-ring core (triterpenes) with various oxygen substituents at different positions. Due to their hydrophobic properties and low solubility in water, they exhibit good antitumor activity when encapsulated in micelles for drug delivery.¹⁸ Cucurbitacins have been shown to have inhibitory effects on leukemia, lymphoma, breast cancer, prostate cancer, lung cancer, liver cancer, uterine cancer, skin cancer, laryngeal cancer, brain cancer, and pancreatic cancer by suppressing the phosphorylation of STAT3 and JAK2. Some cucurbitacins not only inhibit the JAK-STAT signaling pathway but also impact other signaling pathways, such as the MAPK pathway, which are crucial for cancer cell proliferation and survival.¹⁸

In a previous study, the importance of the PI3K/Akt/mTOR and Ras/Raf/MEK/ERK signaling pathways in cell regulation and cancer is highlighted. These pathways are important for cell growth, survival, and metabolism, and problems like mutations can lead to cancer. The complexity of these pathways poses challenges and opportunities for targeted cancer treatments. The PI3K pathway is linked to cell survival and growth, and its dysregulation is common in cancer, making it a treatment target. Inhibitors like idelalisib and copanlisib have been developed for PI3K but may face limitations. The Ras/Raf/MEK/ERK pathway is also vital for growth, with inhibitors like vemurafenib targeting specific mutations. Dual inhibitors for PI3K and other pathways are being

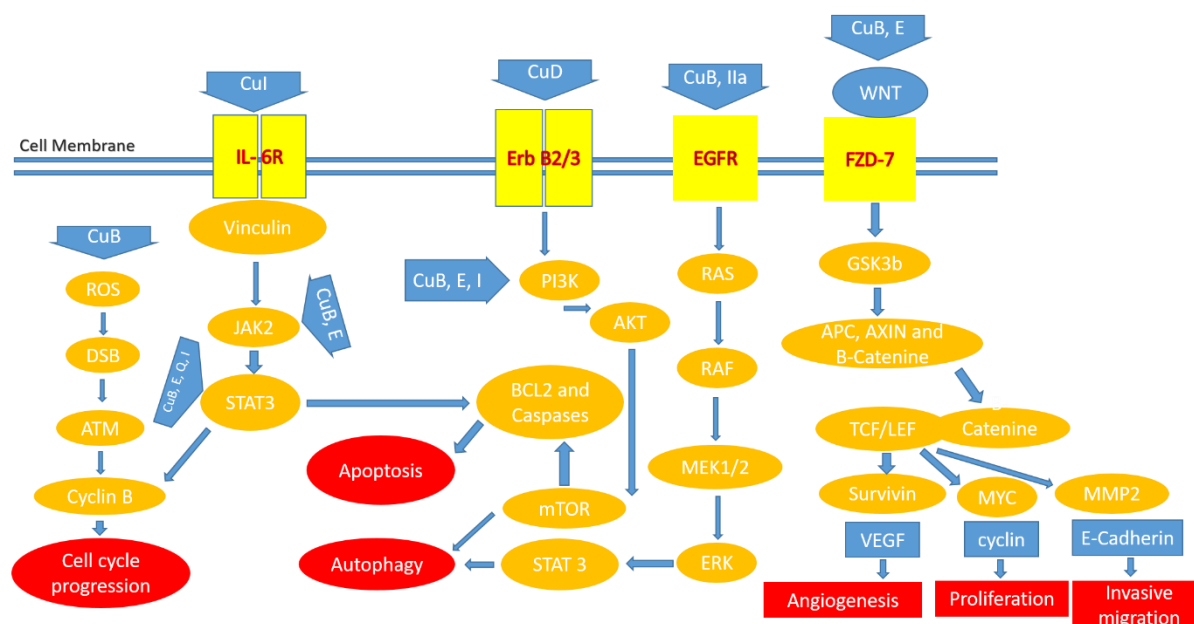


Figure 2. Provides an Overview of the Signaling Pathways Affected by Cucurbitacins. Some pathways lead to apoptosis and autophagy, which are enhanced by cucurbitacins. Other pathways promote cell growth, proliferation, invasion, and angiogenesis, but are inhibited by cucurbitacins. Cu: Cucurbitacin, ROS: Reactive oxygen species,²³ DSB: Disulfide bond protein, ATM: The protein kinase ataxia telangiectasia mutated, JAK: Janus kinase,²⁷ STAT: Signal transducer and activator of transcription protein,^{20,25} PI3K: Phosphoinositide 3-kinases,²² MAPK: Mitogen-activated protein kinase, ERK: Extracellular signal-regulated kinase, IL-6: Interleukin 6,²⁵ Erb: epidermal growth factor receptor, WNT: FDZ-7: Frizzled proteins, GSK3 β : Glycogen synthase kinase-3 beta, APC: Adenomatous polyposis coli, TCF/LEF: T-cell factor/lymphoid enhancer factor, MMP2: matrix metalloproteinase-2, VEGF: Vascular Endothelial Growth Factor.²⁰⁻³⁵

created to improve treatment effectiveness. SAR studies have helped in developing stronger drugs.²³ Cucurbitacins are plant compounds found in pumpkins and gourds that show potential in treating cancer, but their toxicity currently hinders their use. Researchers are working on reducing this toxicity while maximizing their benefits through Structure-Activity Relationship (SAR) studies and molecular modeling. Pharmacokinetic optimization and prodrug strategies are being explored to decrease necessary doses. Targeted delivery systems are also being developed to protect healthy tissues. Preclinical toxicity assessments are crucial before moving on to clinical trials. A collaborative effort involving various scientific disciplines is essential in order to effectively reduce cucurbitacin toxicity.

9. Conclusion

Cucurbitacins are complex triterpene saponins found in the Cucurbitaceae family, primarily consisting of four rings and 30 carbon atoms. They are categorized into 12 groups (A to T) with the main focus on four specific cucurbitacins: B, D, E, and I. These compounds differ in the arrangement of acetyl and hydroxyl groups on carbon atoms, with the cucurbitane core at the center of their molecular structure. Key variations can be found in ring A, side chains, and the presence of unsaturated groups, keto groups, and hydroxyl groups throughout the molecule.

Cucurbitacin B, a compound found in certain plants, has shown potential in combating various types of cancer. In pancreatic cancer, it inhibits proliferation and invasion by affecting MMP-9 and NF- κ B expression, and disrupts the PI3K/Akt/mTOR pathway. In colon cancer, it induces apoptosis and cell cycle arrest, suppresses MMP-7 expression, and targets the Wnt/ β -catenin signaling pathway. For glioblastoma multiforme, Cucurbitacin B inhibits proliferation and invasion by targeting CIP2A and activating the JNK pathway. In osteosarcoma, it reduces bone loss, inhibits the MAPK pathway, suppresses angiogenesis, and hinders metastasis. The effects of Cucurbitacin B on leukemia are still being explored. Overall, Cucurbitacin B shows promising potential as a cancer treatment and preventive agent across multiple types of cancer.

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Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

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